



PATENT
Attorney Docket No. 175931
DHHS Reference No. E-167-1997/0-PCT-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Mitchell et al.

Application No. 09/424,519

Filed: March 3, 2000

For: THE USE OF A NITROXIDE OR A
PRODRUG THEREOF IN THE
PROPHYLACTIC AND THERAPEUTIC
TREATMENT OF CANCER

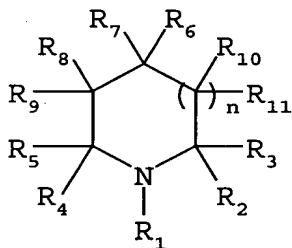
Art Unit: 1614

Examiner: B. Y. S. Kye

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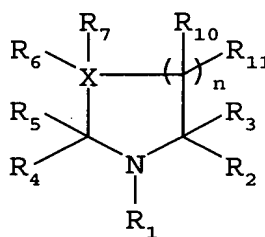
PENDING CLAIMS AFTER AMENDMENTS
MADE IN RESPONSE TO OFFICE ACTION DATED SEPTEMBER 18, 2002

1. A method for the therapeutic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer due to a genetic defect in the *abl*, *bcl2* or *p53* gene a nitroxide or a prodrug thereof in an amount sufficient to treat said cancer, wherein said cancer is susceptible to treatment by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I

or



Formula II

wherein R_1 is selected from the group consisting of H, OH, OZ, O^\cdot , $=O$ and Y, wherein Y is a leaving group, which can be converted to H, OH, O^\cdot or $=O$ by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, wherein R_2 , R_3 , R_4 and R_5 are independently selected from the group consisting of a C_{1-20}

alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R'']_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein, m ≤ 30, and R₂ and R₃ or R₄ and R₅ can be connected through one or more members, each of which is independently selected from the group consisting of carbon and a heteroatom, wherein R₆, R₇, R₈ and R₉ are independently selected from the group consisting of hydrogen, a hydroxyl group, a C₁₋₂₀ aldehydic group, a C₁₋₂₀ keto group, a primary amino group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a sulfamato group, a metal-containing group, a silicone group, a halide, a C₁₋₂₀ ester-containing group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a phosphonato group, a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R'']_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, and m ≤ 30, and wherein any one of R₆, R₇, R₈ and R₉ can be attached covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I, one of R₆ and R₇ and one of R₈ and R₉ can be absent such that a double bond joins the two carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I, and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R₁₀ and R₁₁ are independently selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ aliphatic/aromatic group, a heteroatomic group, a C₁₋₂₀ ether-containing group, a C₁₋₂₀ keto group, a C₁₋₂₀ aldehydic group, a carboxamido group, a cyano group, an amino group, a carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R₁₀ and R₁₁ can be connected

through an aliphatic group and/or an aromatic group, or R_{10} and/or R_{11} can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

4. The method of claim 1, wherein said aliphatic group is branched, substituted and/or unsaturated.

5. The method of claim 4, wherein said aliphatic group is substituted with a member selected from the group consisting of oxygen, phosphorus, selenium, sulfur and nitrogen.

6. The method of claim 1, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

7. The method of claim 6, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

8. The method of claim 1, wherein the metal of said metal-containing group is selected from the group consisting of a transition metal and a lanthanide.

9. The method of claim 6, wherein said aromatic group is substituted.

10. The method of claim 9, wherein said aromatic group is substituted with a heteroatom.

11. The method of claim 10, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

12. The method of claim 1, wherein said alicyclic group is substituted and/or unsaturated.

13. The method of claim 11, wherein said alicyclic group is substituted with a heteroatom.

14. The method of claim 1, wherein said amino group is substituted.

15. The method of claim 14, wherein said amino group is substituted with up to three substituents selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, and a C₁₋₂₀ alicyclic group.

16. The method of claim 15, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

17. The method of claim 16, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

18. The method of claim 15, wherein said aromatic group is substituted.

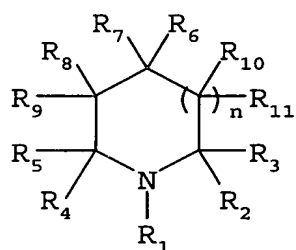
19. The method of claim 18, wherein said aromatic group is substituted with a heteroatom.

20. The method of claim 19, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

21. The method of claim 1, wherein said noncarbon/nonoxygen moiety is selected from the group consisting of boron, sulfur, nitrogen and phosphorus.

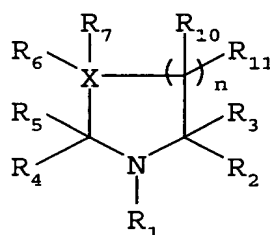
23. The method of claim 1, wherein said genetic defect is the p53 gene.

28. A method for the prophylactic or therapeutic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer due to an inherited genetic defect selected from the group consisting of ataxia telangiectasia, Cowden's disease, Torre's syndrome, Gardner's syndrome, Wiskott-Aldrich syndrome, Peutz-Jeghers syndrome, Bloom's syndrome, Fanconi's syndrome, Wemers syndrome, Chediak-Higashi syndrome, retinoblastoma, Beckwith-Wiedeman syndrome, and neuroblastoma, a nitroxide or a prodrug thereof in an amount sufficient to prevent or treat said cancer, wherein said cancer is susceptible to prevention or treatment by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I

or



Formula II

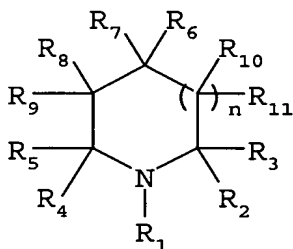
wherein R_1 is selected from the group consisting of H, OH, OZ, O \cdot , =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O \cdot or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, wherein R_2 , R_3 , R_4 and R_5 are independently selected from the group consisting of a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, and $-CH_2-[CR' R'']_m-CH_3$, wherein R' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein, $m \leq 30$, and R_2 and R_3 or R_4 and R_5 can be connected through one or more members, each of which is independently selected from the group consisting of carbon and a heteroatom, wherein R_6 , R_7 , R_8 and R_9 are independently selected from the group consisting

of hydrogen, a hydroxyl group, a C₁₋₂₀ aldehydic group, a C₁₋₂₀ keto group, a primary amino group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a sulfamato group, a metal-containing group, a silicone group, a halide, a C₁₋₂₀ ester-containing group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a phosphonato group, a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R'']_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, and m ≤ 30, and wherein any one of R₆, R₇, R₈ and R₉ can be attached covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I, one of R₆ and R₇ and one of R₈ and R₉ can be absent such that a double bond joins the two carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I, and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R₁₀ and R₁₁ are independently selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ aliphatic/aromatic group, a heteroatomic group, a C₁₋₂₀ ether-containing group, a C₁₋₂₀ keto group, a C₁₋₂₀ aldehydic group, a carboxamido group, a cyano group, an amino group, a carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R₁₀ and R₁₁ can be connected through an aliphatic group and/or an aromatic group, or R₁₀ and/or R₁₁ can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

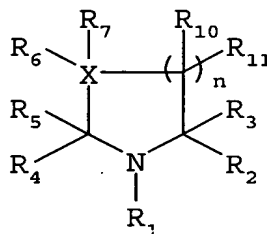
29. The method of claim 28, wherein the inherited genetic defect is ataxia telangiectasia.

30. A method for the prophylactic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer a

nitroxide or a prodrug thereof in an amount sufficient to prevent said cancer, wherein said cancer is susceptible to prevention by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I



Formula II

wherein R_1 is selected from the group consisting of H, OH, OZ, O \cdot , =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O \cdot or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, wherein R_2 , R_3 , R_4 and R_5 are independently selected from the group consisting of a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, and $-CH_2-[CR'R'']_m-CH_3$, wherein R' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein,

$m \leq 30$, and R_2 and R_3 or R_4 and R_5 can be connected through one or more members, each of which is independently selected from the group consisting of carbon and a heteroatom, wherein R_6 , R_7 , R_8 and R_9 are independently selected from the group consisting of hydrogen, a hydroxyl group, a C_{1-20} aldehydic group, a C_{1-20} keto group, a primary amino group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a sulfamato group, a metal-containing group, a silicone group, a halide, a C_{1-20} ester-containing group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a phosphonato group, a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, and -

$\text{CH}_2\text{--}[\text{CR}'\text{R}'']_m\text{--CH}_3$, wherein R' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R'' is selected from the group consisting of hydrogen, a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, and $m \leq 30$, and wherein any one of R_6 , R_7 , R_8 and R_9 can be attached covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I, one of R_6 and R_7 and one of R_8 and R_9 can be absent such that a double bond joins the two carbon atoms to which the remaining R groups are attached, wherein $n = 0\text{--}20$ in Formula I, and $n = 1\text{--}20$ in Formula II, wherein X is a heteroatom, and wherein R_{10} and R_{11} are independently selected from the group consisting of a C_{1-20} aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C_{1-20} aliphatic/aromatic group, a heteroatomic group, a C_{1-20} ether-containing group, a C_{1-20} keto group, a C_{1-20} aldehydic group, a carboxamido group, a cyano group, an amino group, a carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R_{10} and R_{11} can be connected through an aliphatic group and/or an aromatic group, or R_{10} and/or R_{11} can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

31. The method of claim 30, wherein said aliphatic group is branched, substituted and/or unsaturated.

32. The method of claim 31, wherein said aliphatic group is substituted with a member selected from the group consisting of oxygen, phosphorus, selenium, sulfur and nitrogen.

33. The method of claim 30, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

34. The method of claim 33, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

35. The method of claim 30, wherein the metal of said metal-containing group is selected from the group consisting of a transition metal and a lanthanide.

36. The method of claim 33, wherein said aromatic group is substituted.

37. The method of claim 36, wherein said aromatic group is substituted with a heteroatom.

38. The method of claim 37, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

39. The method of claim 30, wherein said alicyclic group is substituted and/or unsaturated.

40. The method of claim 38, wherein said alicyclic group is substituted with a heteroatom.

41. The method of claim 30, wherein said amino group is substituted.

42. The method of claim 41, wherein said amino group is substituted with up to three substituents selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, and a C₁₋₂₀ alicyclic group.

43. The method of claim 42, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

44. The method of claim 43, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

45. The method of claim 42, wherein said aromatic group is substituted.

46. The method of claim 45, wherein said aromatic group is substituted with a heteroatom.

47. The method of claim 46, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

48. The method of claim 30, wherein said noncarbon/nonoxygen moiety is selected from the group consisting of boron, sulfur, nitrogen and phosphorus.

49. The method of claim 30, wherein the cancer is caused by a genetic defect selected from the group consisting of the abl, bcl2 or p53 gene.